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PROVISIONAL APPLICATION COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION under 37 CFR 1.53(c).

Docket Number	50193-168	Type a plus sign (+) inside this box →	+

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TITLE OF THE INVENTION (280 characters max)

BICYCLIC OXAZOLIDINONE ANTIBIOTICS AND DERIVATIVES THEREOF

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BICYCLIC OXAZOLIDINONE ANTIBIOTICS AND DERIVATIVES THEREOF

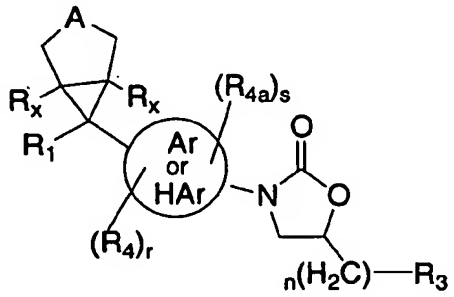
BACKGROUND OF THE INVENTION

Oxazolidinones represent the first new class of antibacterials to be developed since the quinolones. The oxazolidinones are synthetic antibacterial compounds that are orally or intravenously active against problematic multidrug resistant Gram positive organisms and are not cross-resistant with other antibiotics. See Riedl et al, Recent Developments with Oxazolidinone Antibiotics, *Exp. Opin. Ther. Patents* (1999) **9**(5), Ford et al., Oxazolidinones: New Antibacterial Agents, *Trends in Microbiology* **196** Vol.5, No. 5, May 1997 and WO 96/35691.

This invention relates to new oxazolidinones having a cyclopropyl moiety, which are effective against aerobic and anerobic pathogens such as multi-resistant staphylococci, streptococci and enterococci, Bacteroides spp., Clostridia spp. species, as well as acid-fast organisms such as *Mycobacterium tuberculosis* and other mycobacterial species.

SUMMARY OF THE INVENTION

The present invention relates to compounds of formula I:



I

its enantiomer, diastereomer, or pharmaceutically acceptable salt, hydrate or prodrug thereof wherein:

R_1 represents

i) hydrogen,

ii) NR_5R_6,

iii) $CR_7R_8R_9$, $C(R)_2OR_{14}$, CH_2NHR_{14},

iv) $C(=O)R_{13}$, $C(=NOH)H$, $C(=NOR_{13})H$, $C(=NOR_{13})R_{13}$, $C(=NOH)R_{13}$, $C(=O)N(R_{13})_2$, $C(=NOH)N(R_{13})_2$, $NHC(=X_1)N(R_{13})_2$, $(C=NH)R_7$, $N(R_{13})C(=X_1)N(R_{13})_2$, $COOR_{13}$, SO_2R_{14}, $N(R_{13})SO_2R_{14}$, $N(R_{13})COR_{14}$,

v) $(C_{1\text{-}6}alkyl)CN$, CN, $CH=C(R)_2$, $(CH_2)_pOH$, $C(=O)CHR_{13}$, $C(=NR_{13})R_{13}$, $NR_{10}C(=X_1)R_{13}$; or

vi) $C_{5\text{-}10}$ heterocycle optionally substituted with 1-3 groups of R_7, which may be attached through either a carbon or a heteroatom;

A represents NR, O, or S(O)p;

represents aryl or heteroaryl, heterocycle, heterocyclyl or heterocyclic, provided that in the case of a heteroaryl, heterocycle, heterocyclyl or heterocyclic, the cyclopropyl is not attached to a nitrogen atom on the ring;

R_x represents hydrogen or $C_{1\text{-}6}$ alkyl;

R3 represent

i) $NR_{13}(C=X_2)R_{12}$,

ii) $NR_{13}(C=X_1)R_{12}$,

iii) $NR_{13}SO_2R_{14}$,

iv) $N(R_{13})$heteroaryl,

v) $NR_{13}(CHR_{13})_{0\text{-}4}$aryl,

vi) $NR_{13}(CHR_{13})_{0\text{-}4}$heteroaryl,

vii) $S(CHR_{13})_{0\text{-}4}$aryl,

viii) $S(CHR_{13})_{0\text{-}4}$heteroaryl,

ix) $O(CHR_{13})_{0\text{-}4}$aryl,

x) $O(CHR_{13})_{0\text{-}4}$heteroaryl,

xi) $NOH(C=X_1)R_{12}$,

xii) -OC=N(OCOaryl) $C_{1\text{-}6}$ alkyl

xiii) -OC=N(OH) $C_{1\text{-}6}$ alkyl

xiv) C_{5-10} heteroaryl which may be attached through either a carbon or a heteroatom; said aryl and heteroaryl optionally substituted with 1-3 groups of R_7,

R_4, and R_{4a}, independently represent

i) hydrogen,
ii) halogen,
iii) C_{1-6} alkoxy, or
iv) C_{1-6} alkyl

r and s independently are 1-3, with the provision that when $(R_{4a})_s$ and $(R_4)_r$ are attached to an Ar or HAr ring the sum of r and s is less than or equal to 4;

R_5 and R_6 independently represent

i) hydrogen,
ii) C_{1-6} alkyl optionally substituted with 1-3 groups of halogen, CN, OH, C_{1-6} alkoxy, amino, imino, hydroxyamino, alkoxyamino, C_{1-6} acyloxy, C_{1-6} alkylsulfenyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, aminosulfonyl, C_{1-6} alkylaminosulfonyl, C_{1-6} dialkylaminosulfonyl, 4-morpholinylsulfonyl, phenyl, pyridine, 5-isoxazolyl, ethylenyloxy, or ethynyl, said phenyl and pyridine optionally substituted with 1-3 halogen, CN, OH, CF_3, C_{1-6} alkyl or C_{1-6} alkoxy;
iii) C_{1-6} acyl optionally substituted with 1-3 groups of halogen, OH, SH, C_{1-6} alkoxy, naphthalenoxy, phenoxy, amino, C_{1-6} acylamino, hydroxylamino, alkoxylamino, C_{1-6} acyloxy, aralkyloxy, phenyl, pyridine, C_{1-6} alkylcarbonyl, C_{1-6} alkylamino, C_{1-6} dialkylamino, C_{1-6} hydroxyacyloxy, C_{1-6} alkylsulfenyl, phthalimido, maleimido, succinimido, said phenoxy, phenyl and pyridine optionally substituted with 1-3 groups of halo, OH, CN, C_{1-6} alkoxy, amino, C_{1-6} acylamino, CF_3 or C_{1-6} alkyl;
iv) C_{1-6} alkylsulfonyl optionally substituted with 1-3 groups of halogen, OH, C_{1-6} alkoxy, amino, hydroxylamino, alkoxylamino, C_{1-6} acyloxy, or phenyl; said phenyl optionally substituted with 1-3 groups of halo, OH, C_{1-6} alkoxy, amino, C_{1-6} acylamino, CF_3 or C_{1-6} alkyl;
v) arylsulfonyl optionally substituted with 1-3 of halogen, C_{1-6} alkoxy, OH or C_{1-6} alkyl;

vi) C_{1-6} alkoxycarbonyl optionally substituted with 1-3 of halogen, OH, C_{1-6} alkoxy, C_{1-6} acyloxy, or phenyl, said phenyl optionally substituted with 1-3 groups of halo, OH, C_{1-6} alkoxy, amino, C_{1-6} acylamino, CF_3 or C_{1-6} alkyl;

vii) aminocarbonyl, C_{1-6} alkylaminocarbonyl or C_{1-6} dialkylaminocarbonyl, said alkyl groups optionally substituted with 1-3 groups of halogen, OH, C_{1-6} alkoxy or phenyl

viii) five to six membered heterocycles optionally substituted with 1-3 groups of halogen, OH, CN, amino, C_{1-6} acylamino, C_{1-6} alkylsulfonylamino, C_{1-6} alkoxycarbonylamino, C_{1-6} alkoxy, C_{1-6} acyloxy or C_{1-6} alkyl, said alkyl optionally substituted with 1-3 groups of halogen, or C_{1-6} alkoxy;

ix) C_{3-6} cycloalkylcarbonyl optionally substituted with 1-3 groups of halogen, OH, C_{1-6} alkoxy or CN;

x) benzoyl optionally substituted with 1-3 groups of halogen, OH, C_{1-6} alkoxy, C_{1-6} alkyl, CF_3, C_{1-6} alkanoyl, amino or C_{1-6} acylamino;

xi) pyrrolylcarbonyl optionally substituted with 1-3 of C_{1-6} alkyl;

xii) C_{1-2} acyloxyacetyl where the acyl is optionally substituted with amino, C_{1-6} alkylamino, C_{1-6} dialkylamino, 4-morpholino, 4-aminophenyl, 4-(dialkylamino)phenyl, 4-(glycylamino)phenyl; or

R_5 and R_6 taken together with any intervening atoms can form a 3 to 7 membered heterocyclic ring containing carbon atoms and 1-2 heteroatoms independently chosen from O, S, SO, SO_2, N, or NR_8;

R_7 represent

i) hydrogen, halogen, CN, CO_2R, $CON(R)_2$, CHO, CH_2NHAc, C(=NOR), OH, C_{1-6} alkoxy, C_{1-6} alkyl, alkenyl, hydroxy C_{1-6} alkyl, $(CH_2)_{1-3}NHC(O)C_{1-6}$ alkyl, $(CH_2)_{1-3}N(C_{1-6}$ alkyl$)_2$

ii) $(CH_2)_n$amino, $(CH_2)_nC$1-6 alkylamino, C_{1-6} dialkylamino, hydroxylamino or C_{1-2} alkoxyamino all of which can be optionally substituted on the nitrogen with C_{1-6} acyl, C_{1-6} alkylsulfonyl or C_{1-6} alkoxycarbonyl, said acyl and alkylsulfonyl optionally substituted with 1-2 of halogen or OH;

R_8 and R_9 independently represents

i) H, CN,

ii) C_{1-6} alkyl optionally substituted with 1-3 halogen, CN, OH, C_{1-6} alkoxy, C_{1-6} acyloxy, or amino,

iii) phenyl optionally substituted with 1-3 groups of halogen, OH, C_{1-6} alkoxy; or

R_7 and R_8 taken together can form a 3-7 membered carbon ring optionally interrupted with 1-2 heteroatoms chosen from O, S, SO, SO_2, NH, and NR_8;

X_1 represents O, S or NR_{13}, NCN, NCO_2R_{16}, or NSO_2R_{14}

X_2 represents O, S, NH or NSO_2R_{14};

R_{10} represents hydrogen, C_{1-6} alkyl or CO_2R_{15};

R_{12} represents hydrogen, C_{1-6} alkyl, NH_2, OR, CHF_2, $CHCl_2$, CR_2Cl, $(CH_2)_nSR$, $(CH_2)_nCN$, $(CH_2)_nSO_2R$, $(CH_2)_nS(O)R$, C_{1-6} alkylamino, C_{5-10} heteroaryl or C_{1-6} dialkylamino, where said alkyl may be substituted with 1-3 groups of halo, CN, OH or C_{1-6} alkoxy, said heteroaryl optionally substituted with 1-3 groups of R_7;

Each R_{13} represents independently hydrogen, C_{1-6} alkyl, C_{6-10} aryl, NR_5R_6, SR_8, $S(O)R_8$, $S(O)_2R_8$, CN, OH, C_{1-6} alkylS(O)R, C_{1-6} alkoxycarbonyl, hydroxycarbonyl, -OCOaryl, C_{1-6} acyl, C_{3-7} membered carbon ring optionally interrupted with 1-4 heteroatoms chosen from O, S, SO, SO_2, NH and NR_8 where said C_{1-6} alkyl, aryl or C_{1-6} acyl groups may be independently substituted with 0-3 halogens, hydroxy, $N(R)_2$, CO_2R, C_{6-10} aryl, C_{5-10} heteroaryl, or C_{1-6} alkoxy groups;
When two R_{13} groups are attached to the same atom or two adjacent atoms they may be taken together to form a 3-7 membered carbon ring optionally interrupted with 1-2 heteroatoms chosen from O, S, SO, SO_2, NH, and NR_8;

R represents hydrogen, $(CH_2)_pCN$, C_{1-6} alkyl, CO_2C_{1-6} alkyl, $COCH_2OH$, $COCH_2OCOC_{1-6}$ alkyl, SO_2C_{1-6} alkyl;

R_{14} represents amino, C_{1-6} alkyl, C_{1-6} haloalkyl, five to six membered heterocycles or phenyl, said phenyl and heterocycles optionally substituted with 1-3 group of halo, C_{1-6} alkoxy, C_{1-6} acylamino, or C_{1-6} alkyl, hydroxy and/or amino, said amino and hydroxy optionally protected with an amino or hydroxy protecting group;

R_{15} is C_{1-6} alkyl or benzyl said benzyl optionally substituted with 1-3 groups of halo, OH, C_{1-6} alkoxy, amino, C_{1-6} acylamino, or C_{1-6} alkyl;

R_{16} is hydrogen, C_{5-10}heteroaryl, C_{6-10}aryl, said heteroaryl and aryl optionally substituted with 1-3 groups of R_7;

p represents 0-2 and

m, n, and q represents 0-1.

Another aspect of the invention is concerned with the use of the novel antibiotic compositions in the treatment of bacterial infections.

DETAILED DESCRIPTION OF THE INVENTION

The invention is described herein in detail using the terms defined below unless otherwise specified.

The compounds of the present invention may have asymmetric centers, chiral axes and chiral planes, and occur as racemates, racemic mixtures, and as individual diastereomers, with all possible isomers, including optical isomers, being included in the present invention. (See E.L. Eliel and S. H. Wilen Stereochemistry of Carbon Compounds (John Wiley and Sons, New York 1994, in particular pages 1119-1190).

When any variable (e.g. aryl, heterocycle, R_5, R_6 etc.) occurs more than once, its definition on each occurrence is independent at every other occurrence. Also combinations of substituents/or variables are permissible only if such combinations result in stable compounds.

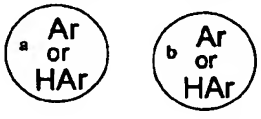
The term "alkyl" refers to a monovalent alkane (hydrocarbon) derived radical containing from 1 to 15 carbon atoms unless otherwise defined. It may be straight or branched. Preferred alkyl groups include lower alkyls which have from 1 to 6 carbon atoms such as methyl, ethyl, propyl, isopropyl, butyl and t-butyl. When substituted, alkyl groups may be substituted with up to 3 substituent groups, selected from the

groups as herein defined, at any available point of attachment. When the alkyl group is said to be substituted with an alkyl group, this is used interchangeably with "branched alkyl group".

Cycloalkyl is a species of alkyl containing from 3 to 15 carbon atoms, without alternating or resonating double bonds between carbon atoms. It may contain from 1 to 4 rings which are fused. Preferred cycloalkyl groups are cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. When substituted, cycloalkyl groups may be substituted with up to 3 substituents which are defined herein by the definition of alkyl.

Alkanoyl refers to a group derived from an aliphatic carboxylic acid of 2 to 4 carbon atoms. Examples are acetyl, propionyl, butyryl and the like.

The term "alkoxy" refers to those groups of the designated length in either a straight or branched configuration and if two or more carbon atoms in length, they may include a double or a triple bond. Exemplary of such alkoxy groups are methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tertiary butoxy, pentoxy, isopentoxy, hexoxy, isohexoxy allyloxy, propargyloxy, and the like.

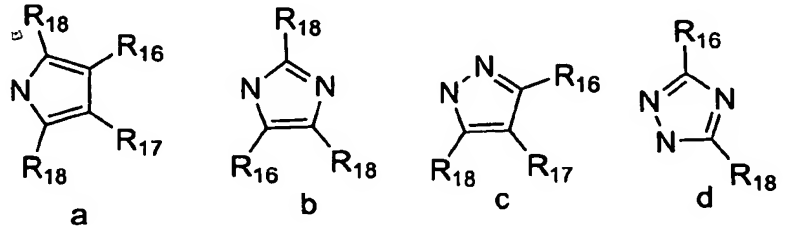


refers to aryl or heteroaryl, heterocycle, Het, heterocyclyl or heterocyclic as described immediately below.

Aryl refers to any stable monocyclic or bicyclic carbon ring of up to 7 atoms in each ring, wherein at least one ring is aromatic. Examples of such aryl elements include phenyl, napthyl, tetrahydronaphthyl, indanyl, indanonyl, biphenyl, tetralilnyl, tetralonyl, fluorenonyl, phenanthryl, anthryl, acenaphthyl, and the like substituted phenyl and the like. Aryl groups may likewise be substituted as defined. Preferred substituted aryls include phenyl and naphthyl.

The term heterocycle, heteroaryl, Het, heterocyclyl or heterocyclic, as used herein except where noted, represents a stable 5- to 7-membered mono- or bicyclic or stable 8- to 11-membered bicyclic heterocyclic ring system, any ring of which may be saturated or unsaturated, and which consists of carbon atoms and from one to four heteroatoms selected from the group consisting of N, O and S, and wherein the nitrogen and sulfur heteroatoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized (in which case it is properly balanced by a counterion), and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached

at any heteroatom or carbon atom, which results in the creation of a stable structure. The term heterocycle or heterocyclic includes heteroaryl moieties. "Heterocycle" or "heterocyclyl" therefore includes the above mentioned heteroaryls, as well as dihydro and tetrahydro analogs thereof. The heterocycle, heteroaryl, Het or heterocyclic may be substituted with 1-3 groups of R7. Examples of such heterocyclic elements include, but are not limited to the following: piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolodinyl, 2-oxoazepinyl, azepinyl, pyrrolyl, 4-piperidonyl, pyrrolidinyl, pyrazolyl, pyrazolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, pyridyl, pyrazinyl, pyrimidinyl, pyrimidonyl, pyridinonyl, pyridazinyl, oxazolyl, oxazolidinyl, isoxazolyl, isoxazolidinyl, morpholinyl, thiazolyl, thiazolidinyl, isothiazolyl, quinuclidinyl, isothiazolidinyl, indolyl, quinolinyl, isoquinolinyl, benzimidazolyl, thiadiazoyl, benzopyranyl, benzothiazolyl, benzoxazolyl, furyl, tetrahydrofuryl, tetrahydropyranyl, thiophenyl, imidazopyridinyl, triazolyl, tetrazolyl, triazinyl, thienyl, benzothienyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, naphthpyridinyl, dihydropyrimidinyl, dihydropyrrolyl, dihydroquinolinyl, dihydrotetrazolyl, dihydrotriazolyl, dihydrothienyl, dihydrooxazolyl, dihydrobenzothiophenyl, dihydrofuranyl, benzothiazolyl, benzothienyl, benzoimidazolyl, benzopyranyl, benzothiofuranyl, carbolinyl, chromanyl, cinnolinyl, benzopyrazolyl, benzodioxolyl and oxadiazolyl. Additional examples of heteroaryls are illustrated by formulas a, b, c and d:



wherein R_{16} and R_{17} are independently selected from hydrogen, halogen, C_{1-6} alkyl, C_{2-4} alkanoyl, C_{1-6} alkoxy; and R_{18} represents hydrogen, C_{1-6} alkyl, C_{2-4} alkanoyl, C_{1-6} alkoxycarbonyl and carbamoyl.

The term "alkenyl" refers to a hydrocarbon radical straight, branched or cyclic containing from 2 to 10 carbon atoms and at least one carbon to carbon double bond. Preferred alkenyl groups include ethenyl, propenyl, butenyl and cyclohexenyl.

The terms "quaternary nitrogen" and "positive charge" refer to tetravalent, positively charged nitrogen atoms (balanced as needed by a counterion known in the art) including, e.g., the positively charged nitrogen in a tetraalkylammonium group (e. g. tetramethylammonium), heteroarylium, (e.g., N-methyl-pyridinium), basic nitrogens which are protonated at physiological pH, and the like. Cationic groups thus encompass positively charged nitrogen-containing groups, as well as basic nitrogens which are protonated at physiologic pH.

The term "heteroatom" means O, S or N, selected on an independent basis.

The term "prodrug" refers to compounds which are drug precursors which, following administration and absorption, release the drug in vivo via some metabolic process. Exemplary prodrugs include acyl amides of the amino compounds of this inventon such as amides of alkanoic(C_{1-6})acids, amides of aryl acids (e.g., benzoic acid) and alkane(C_{1-6})dioic acids.

Halogen and "halo" refer to bromine, chlorine, fluorine and iodine.

When a group is termed "substituted", unless otherwise indicated, this means that the group contains from 1 to 3 substituents thereon.

When a functional group is termed "protected", this means that the group is in modified form to preclude undesired side reactions at the protected site. Suitable protecting groups for the compounds of the present invention will be recognized from the present application taking into account the level of skill in the art, and with reference to standard textbooks, such as Greene, T. W. et al. Protective Groups in Organic Synthesis Wiley, New York (1991). Examples of suitable protecting groups are contained throughout the specification.

Examples of suitable hydroxyl and amino protecting groups are: trimethylsilyl, triethylsilyl, o-nitrobenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, t-butyldiphenylsilyl, t-butyldimethylsilyl, benzyloxycarbonyl, t-butyloxycarbonyl, 2,2,2-trichloroethyloxycarbonyl, allyloxycarbonyl and the like. Examples of suitable carboxyl protecting groups are benzhydryl, o-nitrobenzyl, p-nitrobenzyl, 2-naphthylmethyl, allyl, 2-chloroallyl, benzyl, 2,2,2-trichloroethyl, trimethylsilyl, t-butyldimethylsilyl, t-butldiphenylsilyl, 2-(trimethylsilyl)ethyl, phenacyl, p-methoxybenzyl, acetonyl, p-methoxyphenyl, 4-pyridylmethyl, t-butyl and the like.

The cyclopropyl containing oxazolidinone compounds of the present invention are useful per se and in their pharmaceutically acceptable salt and ester forms for the treatment of bacterial infections in animal and human subjects. The term "pharmaceutically acceptable ester, salt or hydrate," refers to those salts, esters and

hydrated forms of the compounds of the present invention which would be apparent to the pharmaceutical chemist. i.e., those which are substantially non-toxic and which may favorably affect the pharmacokinetic properties of said compounds, such as palatability, absorption, distribution, metabolism and excretion. Other factors, more practical in nature, which are also important in the selection, are cost of the raw materials, ease of crystallization, yield, stability, solubility, hygroscopicity and flowability of the resulting bulk drug. Conveniently, pharmaceutical compositions may be prepared from the active ingredients in combination with pharmaceutically acceptable carriers. Thus, the present invention is also concerned with pharmaceutical compositions and methods of treating bacterial infections utilizing as an active ingredient the novel cyclopropyl containing oxazolidinone compounds.

The pharmaceutically acceptable salts referred to above also include acid addition salts. Thus, when the Formula I compounds are basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic or organic acids. Included among such acid salts are the following: acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, isethionic, lactate, maleate, mandelic, malic, maleic, methanesulfonate, mucic, 2-naphthalenesulfonate, nicotinate, nitric oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, phosphate, pantothenic, pamoic, sulfate, succinate, tartrate, thiocyanate, tosylate and undecanoate.

When the compound of the present invention is acidic, suitable "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium zinc and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium and sodium salts. Salts derived from pharmaceutically acceptable inorganic non-toxic bases include salts of primary, secondary and teritary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as arginine, betaine caffeine, choline, N,N^1-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine,

ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine tripropylamine, tromethamine and the like.

The pharmaceutically acceptable esters are such as would be readily apparent to a medicinal chemist, and include those which are hydrolyzed under physiological conditions, such as "biolabile esters", pivaloyloxymethyl, acetoxymethyl, phthalidyl, indanyl and methoxymethyl, and others.

Biolabile esters are biologically hydrolizable, and may be suitable for oral administration, due to good absorption through the stomach or intenstinal mucosa, resistance to gastric acid degrada-tion and other factors. Examples of biolabile esters include compounds.

An embodiment of this invention is realized when R_1 represents H, NR_5R_6, CN, OH, $C(R)_2OR_{14}$, $NHC(=X1)N(R_{13})_2$, $C(=NOH)N(R_{13})_2$, $NR_{10}C(=X_1)R_{13}$ or $CR_7R_8R_9$ and all other variables are as described herein.

Another embodiment of this invention is realized when 

is phenyl, pyridine, pyrimidine, or piperidine and all other variables are as described herein.

Another embodiment of this invention is realized when one of R_1 is $NR_{10}C(=X_1)R_{13}$ and and all other variables are as described herein.

Another embodiment of this invention is realized when one of R_1 is CN and all other variables are as described herein.

Another embodiment of this invention is realized when one of R_1 NR_5R_6 and all other variables are as described herein.

Another embodiment of this invention is realized when R_3 is $NR(C=X_1)R_{12}$, C_{5-10} heteroaryl, $NH(CH_2)_{0-4}$aryl, $NH(CH_2)_{0-4}$heteroaryl, said aryl and heteroaryl optionally substituted with 1-3 groups of Ra and all other variables are as described herein.

Another embodiment of this invention is realized when R_3 is a C_{5-10} heteroaryl represented by 

which represents an optionally substituted aromatic heterocyclic group containing 1to 4 nitrogen atoms and at least one double bond, and which is connected through a bond on any nitrogen. Exemplary groups are 1,2,3-

triazole, 1,2,4-triazole, 1,2,5-triazole, tetrazole, pyrazole, and imidazole, any of which may contain 1 to 3 substitutents selected from R_7.

Still another embodiment of this invention is realized when R_5 and R_6 independently are:

i) H,

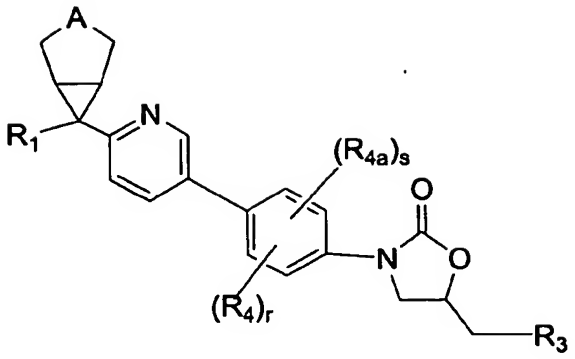
ii) C_{1-6} alkyl optionally substituted with 1-3 groups of halogen, CN, OH, C_{1-6} alkoxy, amino, hydroxyamino, alkoxyamino, C_{1-6} acyloxy, C_{1-6} alkylsulfenyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, aminosulfonyl, C_{1-6} alkylaminosulfonyl, C_{1-6} dialkylaminosulfonyl, 4-morpholinylsulfonyl, phenyl, pyridine, 5-isoxazolyl, ethyenyloxy, or ethynyl, said phenyl and pyridine optionally substituted with 1-3 halogen, CN, OH, CF_3, C_{1-6} alkyl or C_{1-6} alkoxy;

iii) C_{1-6} acyl optionally substituted with 1-3 groups of halogen, OH, SH, C_{1-6} alkoxy, naphthalenoxy, phenoxy, amino, C_{1-6} acylamino, hydroxylamino, alkoxylamino, C_{1-6} acyloxy, phenyl, pyridine, C_{1-6} alkylcarbonyl, C_{1-6} alkylamino, C_{1-6} dialkylamino, C_{1-6} hydroxyacyloxy, C_{1-6} alkylsulfenyl, phthalimido, maleimido, succinimido, said phenoxy, phenyl and pyridine optionally substituted with 1-3 groups of halo, OH, CN, C_{1-6} alkoxy, amino, C_{1-6} acylamino, CF_3 or C_{1-6} alkyl; or

iv) benzoyl optionally substituted with 1-3 groups of halogen, OH, C_{1-6} alkoxy, C_{1-6} alkyl, CF3, C_{1-6} alkanoyl, amino or C_{1-6} acylamino and all other variables are as described herein.

Yet another embodiment of this invention is realized when X_1 represents O and all other variables are as described herein.

A preferred embodiment of this invention is realized when the structural formula is II:



Formula II

wherein R_1, R_4, R_{4a}, Y and R_3 are as described herein.

Preferred compounds of this invention are:
N-[5(S)-3-[4-[(1α,5α,6β)-(6-cyanobicyclo[3.1.0]hexan-6-yl)]phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide,
1-[5(R)-3-[4-[(1α,5α,6β)-(6-cyanobicyclo[3.1.0]hexan-6-yl)]phenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole,
N-[5(S)-3-[4-[(1α,5α,6β)-(3-t-butoxycarbonyl-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl)]phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide,
N-[5(S)-3-[4-[(1α,5α,6β)-(6-cyano-3-azabicyclo[3.1.0]hexan-6-yl)]phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide hydrochloride,
1-[5(R)-3-[4-[(1α,5α,6β)-(3-t-butoxycarbonyl-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl)]phenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole,
1-[5(R)-3-[4-[(1α,5α,6β)-(6-cyano-3-azabicyclo[3.1.0]hexan-6-yl)]phenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole hydrochloride,
N-[5(S)-3-[4-[(1α,5α,6β)-(3-acetoxyacetyl-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl)]phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide,
N-[5(S)-3-[4-[(1α,5α,6β)-(6-cyano-3-hydroxyacetyl-3-azabicyclo[3.1.0]hexan-6-yl)]phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide,
N-[5(S)-3-[4-[(1α,5α,6β)-(6-cyano-3-methanesulfonyl-3-azabicyclo[3.1.0]hexan-6-yl)]phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide,
N-[5(S)-3-[4-[(1α,5α,6β)-(6-cyano-3-methyl-3-azabicyclo[3.1.0]hexan-6-yl)]phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide,

N-[5(S)-3-[4-[(1α,5α,6β)-(3,6-dicyano-3-azabicyclo[3.1.0]hexan-6-yl)]phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide,
N-[5(S)-3-[4-[(1α,5α,6β)-(6-cyano-3-cyanomethyl-3-azabicyclo[3.1.0]hexan-6-yl)]phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide,
5(R)-3-[4-[(1α,5α,6β)-(3-t-butoxycarbonyl-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl)]phenyl]-5-[(isoxazol-3-yl)oxy]methyloxazolidin-2-one,
5(R)-3-[4-[(1α,5α,6β)-(6-cyano-3-azabicyclo[3.1.0]hexan-6-yl)]phenyl]-5-[(isoxazol-3-yl)oxy]methyloxazolidin-2-one hydrochloride,
5(R)-3-[4-[(1α,5α,6β)-(3-t-butoxycarbonyl-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl)]phenyl]-5-[N-(t-butoxycarbonyl)-N-(isoxazol-3-yl)]aminomethyloxazolidin-2-one,
5(R)-3-[4-[(1α,5α,6β)-(6-cyano-3-azabicyclo[3.1.0]hexan-6-yl)]phenyl]-5-[N-(isoxazol-3-yl)]aminomethyloxazolidin-2-one hydrochloride,

or their enantiomer, diastereomer, or pharmaceutically acceptable salt, hydrate or prodrug thereof wherein.

Suitable subjects for the administration of the formulation of the present invention include mammals, primates, man, and other animals. *In vitro* antibacterial activity is predictive of *in vivo* activity when the compositions are administered to a mammal infected with a susceptible bacterial organism.

Using standard susceptibility tests, the compositions of the invention are determined to be active against MRSA and enterococcal infections.

The compounds of the invention are formulated in pharmaceutical compositions by combining the compounds with a pharmaceutically acceptable carrier. Examples of such carriers are set forth below.

The compounds may be employed in powder or crystalline form, in liquid solution, or in suspension. They may be administered by a variety of means; those of principal interest include: topically, orally and parenterally by injection (intravenously or intramuscularly).

Compositions for injection, a preferred route of delivery, may be prepared in unit dosage form in ampules, or in multidose containers. The injectable compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain various formulating agents. Alternatively, the active ingredient may be in powder (lyophilized or non-lyophilized) form for reconstitution at the time of delivery with a suitable vehicle, such as sterile water. In injectable compositions, the carrier is typically comprised of sterile water,

saline or another injectable liquid, e.g., peanut oil for intramuscular injections. Also, various buffering agents, preservatives and the like can be included.

Topical applications may be formulated in carriers such as hydrophobic or hydrophilic bases to form ointments, creams, lotions, in aqueous, oleaginous or alcoholic liquids to form paints or in dry diluents to form powders.

Oral compositions may take such forms as tablets, capsules, oral suspensions and oral solutions. The oral compositions may utilize carriers such as conventional formulating agents, and may include sustained release properties as well as rapid delivery forms.

The dosage to be administered depends to a large extent upon the condition and size of the subject being treated, the route and frequency of administration, the sensitivity of the pathogen to the particular compound selected, the virulence of the infection and other factors. Such matters, however, are left to the routine discretion of the physician according to principles of treatment well known in the antibacterial arts. Another factor influencing the precise dosage regimen, apart from the nature of the infection and peculiar identity of the individual being treated, is the molecular weight of the compound.

The novel antibiotic compositions of this invention for human delivery per unit dosage, whether liquid or solid, comprise from about 0.01% to as high as about 99% of the cyclopropyl containing oxazolidinone compounds discussed herein, the preferred range being from about 10-60% and from about 1% to about 99.99% of one or more of other antibiotics such as those discussed herein, preferably from about 40% to about 90%. The composition will generally contain from about 125 mg to about 3.0 g of the cyclopropyl containing oxazolidinone compounds discussed herein; however, in general, it is preferable to employ dosage amounts in the range of from about 250 mg to 1000 mg and from about 200mg to about 5 g of the other antibiotics discussed herein; preferably from about 250 mg to about 1000 mg. In parenteral administration, the unit dosage will typically include the pure compound in sterile water solution or in the form of a soluble powder intended for solution, which can be adjusted to neutral pH and isotonic.

The invention described herein also includes a method of treating a bacterial infection in a mammal in need of such treatment comprising administering to said mammal the claimed composition in an amount effective to treat said infection.

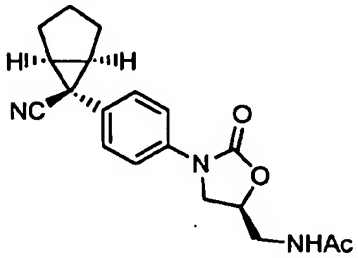
The preferred methods of administration of the claimed compositions include oral and parenteral, e.g., i.v. infusion, i.v. bolus and i.m. injection formulated so that a unit dosage comprises a therapeutically effective amount of each active component or some submultiple thereof.

For adults, about 5-50 mg/kg of body weight, preferably about 250 mg to about 1000 mg per person of the cyclopropyl containing oxazolidinone antibacterial compound and about 250 mg, to about 1000 mg per person of the other antibiotic(s) given one to four times daily is preferred. More specifically, for mild infections a dose of about 250 mg two or three times daily of the cyclopropyl containing oxazolidinone antibacterial compound and about 250 mg two or three times daily of the other antibiotic is recommended. For moderate infections against highly susceptible gram positive organisms a dose of about 500 mg each of the cyclopropyl containing oxazolidinone and the other antibiotics, three or four times daily is recommended. For severe, life-threatening infections against organisms at the upper limits of sensitivity to the antibiotic, a dose of about 500-2000 mg each of the cyclopropyl-containing oxazolidinone compound and the other antibiotics, three to four times daily may be recommended.

For children, a dose of about 5-25 mg/kg of body weight given 2, 3, or 4 times per day is preferred; a dose of 10 mg/kg is typically recommended.

The invention is further described in connection with the following non-limiting examples.

EXAMPLE 1



N-[5(S)-3-[4-[(1α,5α,6β)-(6-Cyanobicyclo[3.1.0]hexan-6-yl)]phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide.

Step 1.

5(R)-3-[4-[(1α,5α,6β)-(6-Cyanobicyclo[3.1.0]hexan-6-yl)]phenyl]-5-hydroxymethyloxazolidin-2-one.

To a solution of 1-benzyloxycarbonylamino-4-[(1α,5α,6β)-(6-cyanobicyclo[3.1.0]hexan-6-yl)]benzene (1.26 g) in dry tetrahydrofuran (25 mL) was added a solution of n-butyllithium in hexane (1.6 M, 2.51 mL) at -78 °C, and the mixture was stirred at the same temperature for 30 min. (R)-Glycidyl butyrate (0.58 mL) was added to the mixture at -78 °C and the mixture was stirred at room temperature for 2 hours. After quenching the reaction with the addition of methanol (2.5 mL), the mixture was stirred at room temperature for 30 minutes. After dilution of the mixture with aqueous ammonium chloride solution, the mixture was extracted with ethyl acetate. The organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and then concentrated in vacuo. Flash chromatography (silica, ethyl acetate) of the residue gave 5(R)-3-[4-[(1α,5α,6β)-(6-cyanobicyclo[3.1.0]hexan-6-yl)]phenyl]-5-hydroxymethyloxazolidin-2-one (995 mg).
MS (EI^+) *m/z*: 298 (M^+).
HRMS (EI^+) for $C_{17}H_{18}N_2O_3$ (M^+): calcd, 298.1317; found, 298.1310.

Step 2.

5(R)-Azidomethyl-3-[4-[(1α,5α,6β)-(6-cyanobicyclo[3.1.0]hexan-6-yl)]phenyl]oxazolidin-2-one.

To a solution of 5(R)-3-[4-[(1α,5α,6β)-(6-cyanobicyclo[3.1.0]hexan-6-yl)]phenyl]-5-hydroxymethyloxazolidin-2-one (298 mg) in dichloromethane (10 mL) was added triethylamine (0.28 mL) and methanesulfonyl chloride (0.12 mL) at 0 °C, the mixture was stirred at the same temperature for 15 minutes. After dilution of the mixture with 1 N hydrochloric acid, the mixture was extracted with ethyl acetate. The organic extracts were washed with water, aqueous sodium hydrogencarbonate solution and brine, dried over anhydrous sodium sulfate, filtered, and then concentrated in vacuo. A suspension of the residue and sodium azide (199 mg) in N,N-dimethylformamide (10 mL) was stirred at 70 °C for 4 hours and concentrated in vacuo. After dilution of the residue with water, the mixture extracted with ethyl acetate. The organic extracts were washed with water and brine, dried over anhydrous sodium sulfate, filtered, and then concentrated in vacuo. Flash chromatography (silica, ethyl acetate) of the residue gave 5(R)-azidomethyl-3-[4-[(1α,5α,6β)-(6-cyanobicyclo[3.1.0]hexan-6-yl)]phenyl]oxazolidin-2-one (304 mg).
MS (EI^+) *m/z*: 323 (M^+).
HRMS (EI^+) for $C_{17}H_{17}N_5O_2$ (M^+): calcd, 323.1382; found, 323.1363.

Step 3.

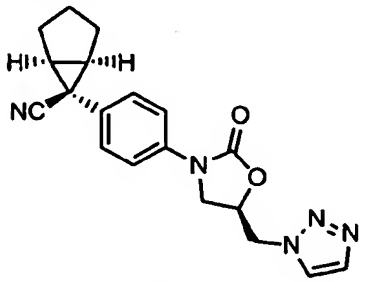
N-[5(S)-3-[4-[(1α,5α,6β)-(6-Cyanobicyclo[3.1.0]hexan-6-yl)]phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide.

A suspension of 5(R)-azidomethyl-3-[4-[(1α,5α,6β)-(6-cyanobicyclo[3.1.0]hexan-6-yl)]phenyl]oxazolidin-2-one (300 mg) and Lindlar catalyst (5% palladium on CaCO3 partially poisoned with lead, 150 mg) in tetrahydrofuran (2 mL) and methanol (10 mL) was hydrogenated at 1 atm for 70 minutes at room temperature. After filtration of the catalyst, the filtrate was concentrated in vacuo to give 5(R)-aminomethyl-3-[4-[(1α,5α,6β)-(6-cyanobicyclo[3.1.0]hexan-6-yl)]phenyl]oxazolidin-2-one (276 mg). This compound was used without further purification. To a solution of the crude 5(R)-aminomethyl-3-[4-[(1α,5α,6β)-(6-cyanobicyclo[3.1.0]hexan-6-yl)]phenyl]oxazolidin-2-one (276 mg) in tetrahydrofuran (10 mL) was added triethylamine (194 μL) and acetic anhydride (108 μL) at 0 °C, and the mixture was stirred at room temperature for 30 minutes. After quenching the reaction by the addition of 1 N hydrochloric acid, the mixture was extracted with ethyl acetate. The organic extracts were washed with water, aqueous sodium hydrogencarbonate solution and brine, dried over anhydrous sodium sulfate, filtered, and then concentrated in vacuo. Flash chromatography (silica, ethyl acetate : methanol = 15:1) of the residue gave N-[5(S)-3-[4-[(1α,5α,6β)-(6-cyanobicyclo[3.1.0]hexan-6-yl)]phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide (276 mg).

MS (EI^+) *m/z*: 339 (M^+).

HRMS (EI^+) for $C_{19}H_{21}N_3O_3$ (M^+): calcd, 339.1583; found, 339.1606.

EXAMPLE 2

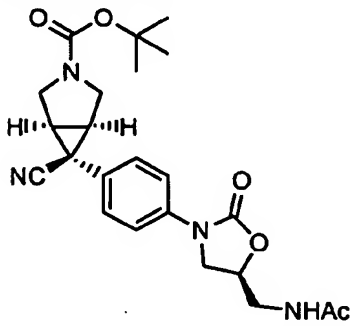


1-[5(R)-3-[4-[(1α,5α,6β)-(6-Cyanobicyclo[3.1.0]hexan-6-yl)]phenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole.

The mixture of 5(R)-azidomethyl-3-[4-[(1α,5α,6β)-(6-cyanobicyclo[3.1.0]hexan-6-yl)]phenyl]oxazolidin-2-one (417 mg) and 2,5-

norbornadiene (0.70 mL) in dioxane (13 mL) was heated under reflux for 4 hours, and then concentrated in vacuo. Flash chromatography (silica, ethyl acetate : methanol = 20:1) of the residue gave 1-[5(R)-3-[4-[(1α,5α,6β)-(6-cyanobicyclo[3.1.0]hexan-6-yl)]phenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole (345 mg).
MS (EI^+) *m/z*: 349 (M^+).
HRMS (EI^+) for $C_{19}H_{19}FN_5O_2$ (M^+): calcd, 349.1539; found, 349.1526.

EXAMPLE 3



N-[5(S)-3-[4-[(1α,5α,6β)-(3-t-Butoxycarbonyl-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl)]phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide.

Step 1.

5(R)-3-[4-[(1α,5α,6β)-(3-t-Butoxycarbonyl-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl)]phenyl]-5-hydroxymethyloxazolidin-2-one.

The title compound 5(R)-3-[4-[(1α,5α,6β)-(3-t-butoxycarbonyl-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl)]phenyl]-5-hydroxymethyloxazolidin-2-one (102 mg) was prepared from 4-[(1α,5α,6β)-(3-t-butoxycarbonyl-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl)]-1-benzyloxycarbonylaminobenzene (123 mg) in the same manner as described for EXAMPLE 1.
MS (EI^+) *m/z*: 399 (M^+).
HRMS (EI^+) for $C_{21}H_{25}N_3O_5$ (M^+): calcd, 399.1794; found, 399.1801.

Step 2.

N-[5(S)-3-[4-[(1α,5α,6β)-(3-t-Butoxycarbonyl-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl)]phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide.

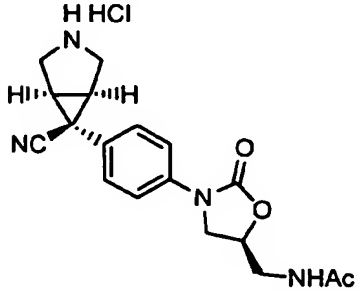
The title compound N-[5(S)-3-[4-[(1α,5α,6β)-(3-t-butoxycarbonyl-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl)]phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide (89.9 mg) was prepared from 5(R)-3-[4-[(1α,5α,6β)-(3-t-butoxycarbonyl-6-cyano-3-

azabicyclo[3.1.0]hexan-6-yl)]phenyl]-5-hydroxymethyloxazolidin-2-one (98.4 mg) in the same manner as described for EXAMPLE 1.

MS (EI$^+$) *m/z*: 440 (M$^+$).

HRMS (EI$^+$) for $C_{23}H_{28}N_4O_5$ (M$^+$): calcd, 440.2060; found, 440.2076.

EXAMPLE 4



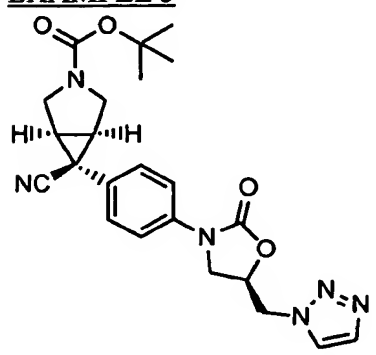
N-[5(S)-3-[4-[(1α,5α,6β)-(6-Cyano-3-azabicyclo[3.1.0]hexan-6-yl)]phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide Hydrochloride.

To a solution of N-[5(S)-3-[4-[(1α,5α,6β)-(3-t-butoxycarbonyl-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl)]phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide (378 mg) in tetrahydrofuran (5 mL) was added a solution of hydrogen chloride in ethanol (10 M, 15 mL) at 0 °C, the mixture was stirred at room temperature for 3 hours and concentrated in vacuo. Treatment with ethanol of the residue gave N-[5(S)-3-[4-[(1α,5α,6β)-(6-cyano-3-azabicyclo[3.1.0]hexan-6-yl)]phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide hydrochloride (275 mg).

MS (EI$^+$) *m/z*: 340 (M$^+$) (as free base).

HRMS (EI$^+$) for $C_{18}H_{20}N_4O_3$ (M$^+$): calcd, 340.1535; found, 340.1553.

EXAMPLE 5



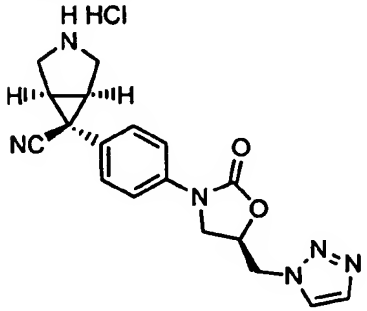
1-[5(R)-3-[4-[(1α,5α,6β)-(3-t-Butoxycarbonyl-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl)]phenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole.

The title compound 1-[5(R)-3-[4-[(1α,5α,6β)-(3-t-butoxycarbonyl-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl)]phenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole (358 mg) was prepared from 5(R)-azidomethyl-3-[4-[(1α,5α,6β)-(3-t-butoxycarbonyl-6-cyanobicyclo[3.1.0]hexan-6-yl)]phenyl]oxazolidin-2-one (425 mg) in the same manner as described for EXAMPLE 2.

MS (FAB^+) *m/z*: 451 (MH^+).

HRMS (FAB^+) for $C_{23}H_{27}FN_6O_4$ (MH^+): calcd, 451.2094; found, 451.2098.

EXAMPLE 6



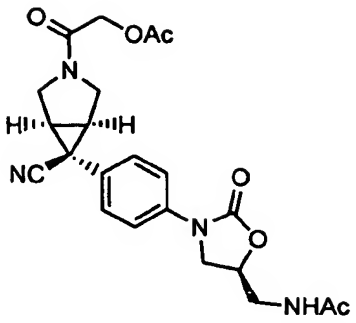
1-[5(R)-3-[4-[(1α,5α,6β)-(6-Cyano-3-azabicyclo[3.1.0]hexan-6-yl)]phenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole Hydrochloride.

1-[5(R)-3-[4-[(1α,5α,6β)-(6-cyano-3-azabicyclo[3.1.0]hexan-6-yl)]phenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole hydrochloride (267 mg) was prepared from 1-[5(R)-3-[4-[(1α,5α,6β)-(3-t-butoxycarbonyl-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl)]phenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole (358 mg) in the same manner as described for EXAMPLE 4.

MS (EI^+) *m/z*: 350 (M^+) (as free base).

HRMS (EI^+) for $C_{18}H_{18}N_6O_2$ (M^+): calcd, 350.1491; found, 350.1464.

EXAMPLE 7



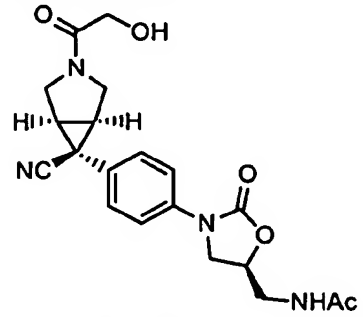
N-[5(S)-3-[4-[(1α,5α,6β)-(3-Acetoxyacetyl-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl)]phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide.

To a suspension of N-[5(S)-3-[4-[(1α,5α,6β)-(6-cyano-3-azabicyclo[3.1.0]hexan-6-yl)]phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide hydrochloride (415 mg) in dichloromethane (11 mL) was added triethylamine (0.46 mL) and acetoxyacetyl chloride (0.15 mL) at 0 °C, the mixture was stirred at the same temperature for 45 minutes. After dilution of the mixture with water, the mixture was extracted with dichloromethane. The organic extracts were dried over anhydrous sodium sulfate, filtered, and then concentrated in vacuo. Flash chromatography (silica, dichloromethane : methanol = 10:1) of the residue gave N-[5(S)-3-[4-[(1α,5α,6β)-(3-acetoxyacetyl-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl)]phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide (378 mg).

MS (FAB$^+$) *m/z*: 441 (MH$^+$).

HRMS (FAB$^+$) for $C_{22}H_{25}N_4O_6$ (MH$^+$): calcd, 441.1774; found, 441.1764.

EXAMPLE 8



N-[5(S)-3-[4-[(1α,5α,6β)-(6-Cyano-3-hydroxyacetyl-3-azabicyclo[3.1.0]hexan-6-yl)]phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide.

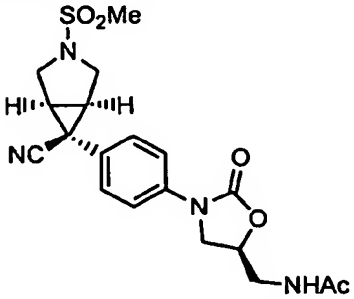
To a suspension of N-[5(S)-3-[4-[(1α,5α,6β)-(3-acetoxyacetyl-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl)]phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide (225

mg) in methanol (5 mL) and tetrahydrofuran (1 mL) was added potassium carbonate (141 mg) at room temperature, the mixture was stirred at the same temperature for 90 minutes and concentrated in vacuo. Flash chromatography (silica, dichloromethane : methanol = 20:1) of the residue gave N-[5(S)-3-[4-[(1α,5α,6β)-(6-cyano-3-hydroxyacetyl-3-azabicyclo[3.1.0]hexan-6-yl)]phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide (138 mg).

MS (FAB$^+$) *m/z*: 399 (MH$^+$).

HRMS (FAB$^+$) for $C_{20}H_{23}N_4O_5$ (MH$^+$): calcd, 399.1668; found, 399.1681.

EXAMPLE 9



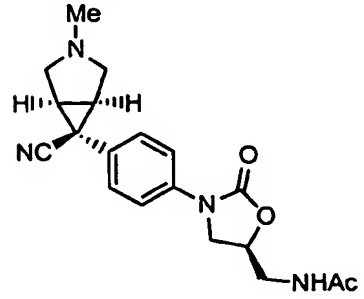
N-[5(S)-3-[4-[(1α,5α,6β)-(6-Cyano-3-methanesulfonyl-3-azabicyclo[3.1.0]hexan-6-yl)]phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide.

The title compound N-[5(S)-3-[4-[(1α,5α,6β)-(6-cyano-3-methanesulfonyl-3-azabicyclo[3.1.0]hexan-6-yl)]phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide (219 mg) was prepared from N-[5(S)-3-[4-[(1α,5α,6β)-(6-cyano-3-azabicyclo[3.1.0]hexan-6-yl)]phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide hydrochloride (226 mg) and methanesulfonyl chloride (70 μL) in the same manner as described for EXAMPLE 7.

MS (FAB$^+$) *m/z*: 419 (MH$^+$).

HRMS (FAB$^+$) for $C_{19}H_{23}N_4O_5S$ (MH$^+$): calcd, 419.1389; found, 419.1386.

EXAMPLE 10



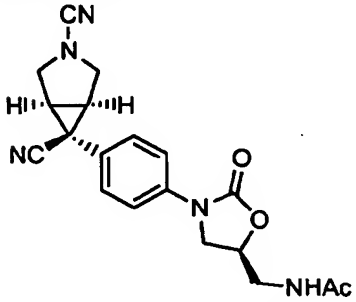
N-[5(S)-3-[4-[(1α,5α,6β)-(6-Cyano-3-methyl-3-azabicyclo[3.1.0]hexan-6-yl)]phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide.

To a suspension of N-[5(S)-3-[4-[(1α,5α,6β)-(6-cyano-3-azabicyclo[3.1.0]hexan-6-yl)]phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide hydrochloride (188 mg) in tetrahydrofuran (5 mL) was added acetic acid (57 μL), 35 % formaldehyde (396 μL), and sodium triacetoxyborohydride (223 mg) at room temperature, the mixture was stirred at the same temperature for 2 hours. After quenching the reaction by addition of aqueous sodium hydrogencarbonate solution, the mixture was extracted with dichloromethane-methanol (5:1). The organic extracts were dried over anhydrous sodium sulfate, filtered, and then concentrated in vacuo. Flash chromatography (silica, dichloromethane : methanol = 10:1) of the residue gave N-[5(S)-3-[4-[(1α,5α,6β)-(6-cyano-3-methyl-3-azabicyclo[3.1.0]hexan-6-yl)]phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide (104 mg).

MS (FAB$^+$) *m/z*: 355 (MH$^+$).

HRMS (FAB$^+$) for $C_{19}H_{23}N_4O_3$ (MH$^+$): calcd, 355.1770; found, 355.1775.

EXAMPLE 11

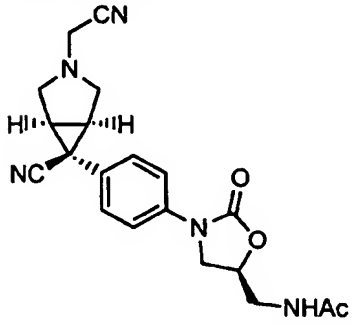


N-[5(S)-3-[4-[(1α,5α,6β)-(3,6-Dicyano-3-azabicyclo[3.1.0]hexan-6-yl)]phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide.

A suspension of N-[5(S)-3-[4-[(1α,5α,6β)-(6-cyano-3-azabicyclo[3.1.0]hexan-6-yl)]phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide hydrochloride (245 mg) and sodium acetate (373 mg) in methanol (22 mL) was stirred at room temperature for 20 minutes. To the resulting suspension was added a solution of cyanogens bromide in dichloromethane (5 M, 0.26 mL) at 0°C, the mixture was stirred at the same temperature for 40 minutes, and concentrated in vacuo. Flash chromatography (silica, dichloromethane : methanol = 10:1) of the residue gave N-[5(S)-3-[4-[(1α,5α,6β)-(3,6-dicyano-3-azabicyclo[3.1.0]hexan-6-yl)]phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide (207 mg).

MS (FAB$^+$) *m/z*: 366 (MH$^+$).
HRMS (FAB$^+$) for $C_{19}H_{20}N_5O_3$ (MH$^+$): calcd, 366.1566; found, 366.1575.

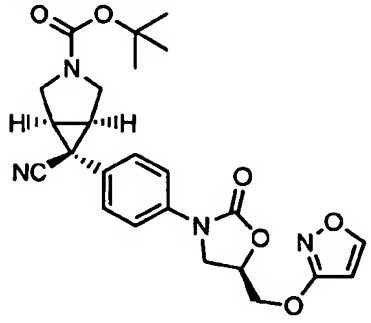
EXAMPLE 12



N-[5(S)-3-[4-[(1α,5α,6β)-(6-Cyano-3-cyanomethyl-3-azabicyclo[3.1.0]hexan-6-yl)]phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide.

A suspension of N-[5(S)-3-[4-[(1α,5α,6β)-(6-cyano-3-azabicyclo[3.1.0]hexan-6-yl)]phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide hydrochloride (245 mg), sodium hydrogencarbonate (273 mg) in N,N-dimethylformamide (6.5 mL) was stirred at room temperature for 10 minutes. To the resulting suspension was added bromoacetonitrile (70 μL) at room temperature, the mixture was stirred at the same temperature for 6 hours, and concentrated in vacuo. Flash chromatography (silica, dichloromethane : methanol = 10:1) of the residue gave N-[5(S)-3-[4-[(1α,5α,6β)-(6-cyano-3-cyanomethyl-3-azabicyclo[3.1.0]hexan-6-yl)]phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide (219 mg).
MS (FAB$^+$) *m/z*: 380 (MH$^+$).
HRMS (FAB$^+$) for $C_{20}H_{22}N_5O_3$ (MH$^+$): calcd, 380.1723; found, 380.1728.

EXAMPLE 13



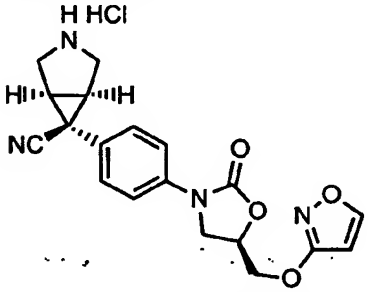
5(R)-3-[4-[(1α,5α,6β)-(3-t-Butoxycarbonyl-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl)]phenyl]-5-[(isoxazol-3-yl)oxy]methyloxazolidin-2-one.

To a suspension of 5(R)-3-[4-[(1α,5α,6β)-(3-t-butoxycarbonyl-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl)]phenyl]-5-hydroxymethyloxazolidin-2-one (10.0 mg), 3-hydroxyisoxazole (4.3 mg) and triphenylphosphine (13.5 mg) in tetrahydrofuran (0.25 mL) was added diisopropyl azodicarboxylate (9.8 μL), the mixture was stirred at room temperature for 3 hours, and concentrated in vacuo. Flash chromatography (silica, hexane : ethyl acetate = 1:5) of the residue gave 5(R)-3-[4-[(1α,5α,6β)-(3-t-butoxycarbonyl-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl)]phenyl]-5-[(isoxazol-3-yl)oxy]methyloxazolidin-2-one (11.7 mg).

MS (FAB^+) *m/z*: 467 (MH^+).

HRMS (FAB^+) for $C_{24}H_{27}N_4O_6$ (MH^+): calcd, 467.1931; found, 467.1903.

EXAMPLE 14



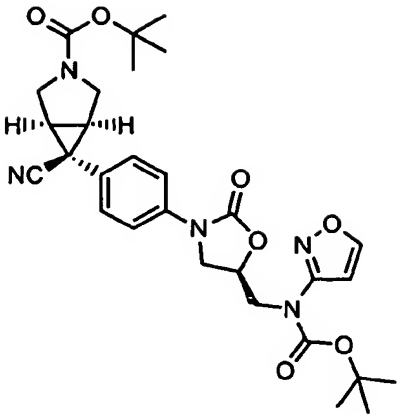
5(R)-3-[4-[(1α,5α,6β)-(6-Cyano-3-azabicyclo[3.1.0]hexan-6-yl)]phenyl]-5-[(isoxazolyl-3-yl)oxy]methyloxazolidin-2-one Hydrochloride.

The title compound 5(R)-3-[4-[(1α,5α,6β)-(6-cyano-3-azabicyclo[3.1.0]hexan-6-yl)]phenyl]-5-[(isoxazolyl-3-yl)oxy]methyloxazolidin-2-one hydrochloride (199 mg) was prepared from 5(R)-3-[4-[(1α,5α,6β)-(3-t-butoxycarbonyl-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl)]phenyl]-5-[(isoxazolyl-3-yl)oxy]methyloxazolidin-2-one (248 mg) in the same manner as described for EXAMPLE 4.

MS (EI^+) *m/z*: 366 (M^+) (as free base).

HRMS (EI^+) for $C_{19}H_{18}N_4O_4$ (M^+): calcd, 366.1328; found, 366.1330.

EXAMPLE 15



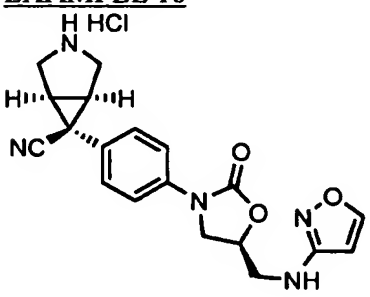
5(R)-3-[4-[(1α,5α,6β)-(3-t-Butoxycarbonyl-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl)]phenyl]-5-[N-(t-butoxycarbonyl)-N-(isoxazol-3-yl)]aminomethyloxazolidin-2-one.

To a suspension of 5(R)-3-[4-[(1α,5α,6β)-(3-t-butoxycarbonyl-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl)]phenyl]-5-hydroxymethyloxazolidin-2-one (10.0 mg), 3-N-(t-butoxycarbonyl)aminoisoxazole (9.2 mg), and tetramethylazodicarboxamide (8.6 mg) in benzene (0.25 mL) was added tributylphosphine (12.5 μL), and the mixture was stirred at room temperature for 90 minutes. After dilution of the mixture with ethyl acetate, the insoluble materials were filtered off, and the filtrate was concentrated in vacuo. Flash chromatography (silica, hexane : ethyl acetate = 3:5) of the mixture gave 5(R)-3-[4-[(1α,5α,6β)-(3-t-butoxycarbonyl-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl)]phenyl]-5-[N-(t-butoxycarbonyl)-N-(isoxazol-3-yl)]aminomethyloxazolidin-2-one (14.1 mg).

MS (FAB^+) *m/z*: 566 (MH^+).

HRMS (FAB^+) for $C_{29}H_{36}N_5O_7$(MH^+): calcd, 566.2615; found, 566.2609.

EXAMPLE 16



5(R)-3-[4-[(1α,5α,6β)-(6-Cyano-3-azabicyclo[3.1.0]hexan-6-yl)]phenyl]-5-[N-(isoxazol-3-yl)]aminomethyloxazolidin-2-one Hydrochloride.

The title compound 5(R)-3-[4-[(1α,5α,6β)-(6-cyano-3-azabicyclo[3.1.0]hexan-6-yl)]phenyl]-5-[N-(isoxazol-3-yl)]aminomethyloxazolidin-2-one hydrochloride (207 mg) was prepared from (R)-3-[4-[(1α,5α,6β)-(3-t-butoxycarbonyl-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl)]phenyl]-5-[N-(t-butoxycarbonyl)-N-(isoxazol-3-yl)]aminomethyloxazolidin-2-one (292 mg) in the same manner as described for EXAMPLE 4.

MS (EI^+) *m/z*: 365 (M^+) (as free base).

HRMS (EI^+) for $C_{19}H_{19}N_5O_3$ (M^+): calcd, 365.1488; found, 365.1478.

REFERENCE EXAMPLE 1

4-[(1α,5α,6β)-(6-Cyanobicyclo[3.1.0]hexan-6-yl)]-1-benzyloxycarbonylaminobenzene.

Step 1.

(1α,5α,6β)-(6-Cyanobicyclo[3.1.0]hexan-6-yl)benzene.

To a solution of lithium diisopropylamide (prepared from diisopropylamine (3.88 mL) and n-butyllithium (1.6 M solution in hexane, 17.4 mL)) in tetahydrofuran (37 mL) was added phenylacetonitrile (3.18 mL) at –50 °C, the mixture was stirred at 0 °C for 3 hours. To the mixture was added a solution of cyclopenten-1-yl phenyl sulfone (5.49 g) in tetrahydrofuran (26 mL) at 5 °C, the mixture was stirred at the same temperature for 40 minutes, and stirred at room temperature for 18 hours. The mixture was stirred at 60 °C for 3 hours. After dilution of the mixture with aqueous ammonium chloride solution, the mixture was extracted with ethyl acetate. The organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and then concentrated in vacuo. Flash chromatography (silica, hexane : ethyl acetate = 10:1) of the residue gave (1α,5α,6β)-(6-cyanobicyclo[3.1.0]hexan-6-yl)benzene (4.44 g).

MS (EI^+) *m/z*: 183 (M^+).

HRMS (EI^+) for $C_{13}H_{13}N$ (M^+): calcd, 183.1048; found, 183.1072.

Step 2.

4-(1α,5α,6β)-(6-cyanobicyclo[3.1.0]hexan-6-yl)-1-nitrobenzene.

To a solution of (1α,5α,6β)-(6-cyanobicyclo[3.1.0]hexan-6-yl)benzene (916 mg) in chloroform (5 mL) was added concentrated sulfuric acid (1.93 mL) and nitric acid (fuming, 0.28 mL) at –30 °C, the mixture was stirred at the same temperature for

1 minute. The mixture was poured into ice water, extracted with chloroform. The organic extracts were washed with aqueous sodium hydrogencarbonate solution and brine, dried over anhydrous sodium sulfate, filtered, and then concentrated in vacuo. Flash chromatography (silica, hexane : ethyl acetate = 10:3) of the residue gave 4-(1α,5α,6β)-(6-cyanobicyclo[3.1.0]hexan-6-yl)-1-nitrobenzene (875 mg).
MS (EI^+) *m/z*: 228 (M^+).
HRMS (EI^+) for $C_{13}H_{12}N_2O_2$ (M^+): calcd, 228.0899; found, 228.0889.

Step 3.

1-Benzyloxycarbonylamino-4-[(1α,5α,6β)-(6-cyanobicyclo[3.1.0]hexan-6-yl)]benzene.

A suspension of 4-(1α,5α,6β)-(6-cyanobicyclo[3.1.0]hexan-6-yl)-1-nitrobenzene (875 mg) and palladium catalyst (10 % on chacoal, 87 mg) in tetrahydrofuran (19 mL) was hydrogenated at 1 atm for 3 hours at room temperature. After filtration of the catalyst, the filtrate was concentrated in vacuo to give 1-amino-4-(1α,5α,6β)-(6-cyanobicyclo[3.1.0]hexan-6-yl)benzene. To a solution of crude 1-amino-4-(1α,5α,6β)-(6-cyanobicyclo[3.1.0]hexan-6-yl)benzene thus obtained in acetone (12 mL) was added sodium hydrogencarbonate (644 mg), water (6 mL) and benzyl chloroformate (0.69 mL) at 0 °C, the mixture was stirred at the same temperature for 5 minutes. After dilution of the mixture by addition of ice water, the mixture was extracted with ethyl acetate. The organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and then concentrated in vacuo. Flash chromatography (silica, hexane: ethyl acetate = 5:2) of the residue gave 1-benzyloxycarbonylamino-4-[(1α,5α,6β)-(6-cyanobicyclo[3.1.0]hexan-6-yl)]benzene (1.27 g).
MS (EI^+) *m/z*: 332 (M^+).
HRMS (EI^+) for $C_{21}H_{20}N_2O_2$ (M^+): calcd, 332.1525; found, 332.1543.

REFERENCE EXAMPLE 2

1-t-Butoxycarbonyl-3-pyrrolin-3-yl phenyl sulfone.

To a suspension of N-chlorosuccinimide (781 mg) in dichloromethane (6 mL) was added benzenethiol (0.60 mL) at room temperature, the mixture was stirred at the same temperature for 30 minutes. To the resulting mixture was added a solution of 1-t-butoxycarbonyl-3-pyrroline (1.00 g) in dichloromethane (1 mL) at –60 °C, the mixture was stirred at room temperature for 1 hour. The insoluble materials were filtered off, the filtrate was concentrated in vacuo. To a solution of the residue in

dichloromethane (29 mL) was added m-chloroperoxybenzoic acid (3.65 g) at 0 °C, the mixture was stirred at room temperature for 1 hour. To the resulting mixture was added sodium carbonate (2.19 g), the mixture was stirred at room temperature for 5 minutes. The insoluble materials were filtered off, the filtrate was diluted with ether. The filtrate was washed with 10 % sodium bisulfate solution, 10 % sodium carbonate solution and brine, dried over anhydrous sodium sulfate, filtered, and then concentrated in vacuo. To a solution of the residue in dichloromethane (11 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (0.92 mL) at –40 °C, the mixture was stirred at room temperature for 5 minutes. The mixture was poured into 1 N hydrochloric acid and extracted with ether. The organic extracts were washed with water, aqueous sodium hydrogencarbonate solution and brine, dried over anhydrous sodium sulfate, filtered, and then concentrated in vacuo. Flash chromatography (silica, hexane: ethyl acetate = 5:2) of the residue gave 1-t-butoxycarbonyl-3-pyrrolin-3-yl phenyl sulfone (1.16 g).

MS (EI^+) *m/z*: 309 (M^+).

HRMS (EI^+) for $C_{15}H_{19}NO_4S$ (M^+): calcd, 309.1035; found, 309.1042.

REFERENCE EXAMPLE 3

1-[(1α,5α,6β)-(3-t-Butoxycarbonyl-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl)]-4-nitrobenzene.

Step 1.

(1α,5α,6β)-(3-t-Butoxycarbonyl-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl)benzene.

The title compound (1α,5α,6β)-(3-t-butoxycarbonyl-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl)benzene (3.83 g) was prepared from phenylacetonitrile (1.65 mL) and 1-t-butoxycarbonyl-3-pyrrolin-3-yl phenyl sulfone (4.46 g) in the same manner as described for REFERENCE EXAMPLE 1.

MS (CI^+) *m/z*: 285 (MH^+).

HRMS (CI^+) for $C_{17}H_{21}N_2O_2$ (MH^+): calcd, 285.1603; found, 285.1616.

Step 2.

1-[(1α,5α,6β)-(6-Cyano-3-trifluoroacetyl-3-azabicyclo[3.1.0]hexan-6-yl)]-4-nitrobenzene.

To a solution of (1α,5α,6β)-(3-butoxycarbonyl-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl)benzene (853 mg) in dichloromethane (7 mL) was added trifluoroacetic acid (7 mL) at 0 °C, the mixture was stirred at room temperature for 75

minutes and concentrated in vacuo. To a solution of the residue in dichloromethane (7 mL) was added triethylamine (5.01 mL) and trifluoroacetic anhydride (1.06 mL) at 0 °C, the mixture was stirred at room temperature overnight and concentrated in vacuo. After dilution of the residue with ethyl acetate, the mixture was washed with 1 N hydrochloric acid, water, aqueous sodium hydrogencarbonate solution and brine, dried over anhydrous sodium sulfate, filtered, and then concentrated in vacuo. To a solution of the residue in chloroform (3 mL) was added ammonium nitrate (372 mg) and trifluoroacetic anhydride (2.19 mL), the mixture was stirred at room temperature for 2.7 hours. After addition of ice, the resulting precipitates were collected by filtration and washed with water and dichloromethane to give 1-[(1α,5α,6β)-(6-cyano-3-trifluoroacetyl-3-azabicyclo[3.1.0]hexan-6-yl)]-4-nitrobenzene (546 mg).
MS (EI^+) *m/z*: 325 (M^+).
HRMS (EI^+) for $C_{14}H_{10}F_3N_3O_3$ (M^+): calcd, 325.0674; found, 325.0648.

Step 3.

1-[(1α,5α,6β)-(3-t-Butoxycarbonyl-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl)]-4-nitrobenzene.

The mixture of 1-[(1α,5α,6β)-(6-cyano-3-trifluoroacetyl-3-azabicyclo[3.1.0]hexan-6-yl)]-4-nitrobenzene (9.2 mg) and a solution of ammonia in methanol (6.7 M, 0.5 mL) was stirred at room temperature for 21 hours and concentrated in vacuo. To a solution of the residue in tetrahydrofuran (0.5 mL) was added triethylamine (19.7 μL) and di-t-butyl dicarbonate (9.5 mg) at 0 °C, the mixture was stirred at room temperature for 30 minutes. Preparative thin layer chromatography (silica, hexane : ethyl acetate = 4:5) of the residue gave 1-[(1α,5α,6β)-(3-t-butoxycarbonyl-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl)]-4-nitrobenzene (8.7 mg).
MS (EI^+) *m/z*: 329 (M^+).
HRMS (EI^+) for $C_{17}H_{19}N_3O_4$ (M^+): calcd, 329.1376; found, 329.1401.

REFERENCE EXAMPLE 4

1-Benzyloxycarbonylamino-4-[(1α,5α,6β)-(3-t-butoxycarbonyl-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl)]benzene.

The title compound 1-benzyloxycarbonylamino-4-[(1α,5α,6β)-(3-t-butoxycarbonyl-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl)]benzene (127 mg) was prepared from 1-[(1α,5α,6β)-(3-t-butoxycarbonyl-6-cyano-3-azabicyclo[3.1.0]hexan-

6-yl)]-4-nitrobenzene (98.8 mg) in the same manner as described for REFERENCE EXAMPLE 1.

MS (EI^+) *m/z*: 433 (M^+).
HRMS (EI^+) for $C_{25}H_{27}N_3O_4$ (M^+): calcd, 433.2002; found, 433.1989.

Antibacterial Activity

The pharmaceutically-acceptable compounds of the present invention are useful antibacterial agents having a good spectrum of activity in vitro against standard bacterial strains, which are used to screen for activity against pathogenic bacteria. Notably, the pharmaceutically-acceptable compounds of the present invention show activity against vancomycin-resistant enterococci, streptococci including penicillin-resistant *S. pneumoniae* , methicillin-resistant *S. aureus*, *M. catarrhalis*, and *C. pneumoniae*. The antibacterial spectrum and potency of a particular compound may be determined in a standard test system.

The following in vitro results were obtained based on an agar dilution method except for *C. pneumoniae*. The activity is presented as the minimum inhibitory concentration (MIC) .

S. aureus and *M. catarrhalis* were tested on Mueller-Hinton agar, using an approximate inoculum of 1 x 10^4 cfu/spot an incubation temperature of 35 C for 24 hours. The MIC was defined as the lowest concentration at which no visible bacterial growth was observed.

Streptococci and enterococci were tested on Mueller-Hinton agar supplemented with 5 % defibrinated horse blood , using an approximate inoculum of 1 x 10^4 cfu/spot an incubation temperature of 35 C in an atmosphere of 5 % CO_2 for 24 hours. The MIC was defined as the lowest concentration at which no visible bacterial growth was observed.

C. pneumoniae was tested using minimum essential medium supplemented with 10 % heat-inactivated fetal bovine serum, 2 mM L-glutamine, 1 mg/ml cycloheximide and non essential amino acid. HeLa 229 cells were inoculated with 10^4 inclusion-forming units of *C. pneumoniae* strain per mL. Infected cells were incubated with test compounds in complete medium at 35 C in an atmosphere of 5 % CO_2 for 72 hours. Cells monolayers were fixed in methanol, stained for chlamydial inclusions with a fluorescein-conjugated anti-Chlamydia monoclonal antibody, and

were observed with fluorescence microscope. The MIC was defined as the lowest concentration at which no inclusion was observed.

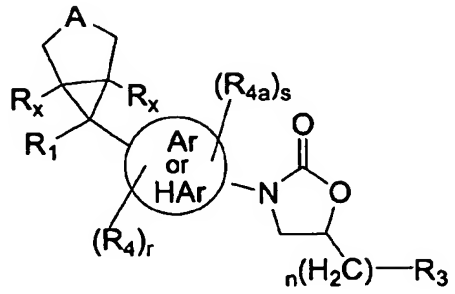
Strains	MIC (μg/ml)				
	example 1	example 8	example 9	example 11	Linezolid
Staphylococcus aureus					
Smith	0.25	1	0.5	0.25	1
CR	2	2	1	1	16
MR	0.25	1	0.5	0.5	1
Streptococcus pneumoniae					
IID553	0.5	0.5	0.5	0.25	2
PRQR	0.25	0.5	0.5	0.25	1
Streptococcus pyogenes					
IID692	0.5	0.5	0.5	0.125	1
Enterococcus faecium					
VRQR	0.25	0.5	0.5	0.25	2
Moraxella catarrhalis					
ATCC25238	0.5	2	2	1	4

CR = chloramphenicol resistant
MR = methicillin resistant
PRQR = penicillin resistant, quinolone resistant
VRQR = vancomycin resistant, quinolone resistant
NT = not tested

The invention described herein is exemplified by the following non-limiting examples. The compound data is designated in accordance to *General Guidelines for Manuscript Preparation*, J. Org. Chem. Vol. 66, pg. 19A, Issue 1, 2001.

WHAT IS CLAIMED IS:

1. The present invention relates to compounds of formula I:



I

its enantiomer, diastereomer, or pharmaceutically acceptable salt, hydrate or prodrug thereof wherein:

R_1 represents

vi) hydrogen,

vii) NR_5R_6,

viii) $CR_7R_8R_9$, $C(R)_2OR_{14}$, CH_2NHR_{14},

ix) $C(=O)R_{13}$, $C(=NOH)H$, $C(=NOR_{13})H$, $C(=NOR_{13})R_{13}$, $C(=NOH)R_{13}$, $C(=O)N(R_{13})_2$, $C(=NOH)N(R_{13})_2$, $NHC(=X_1)N(R_{13})_2$, $(C=NH)R_7$, $N(R_{13})C(=X_1)N(R_{13})_2$, $COOR_{13}$, SO_2R_{14}, $N(R_{13})SO_2R_{14}$, $N(R_{13})COR_{14}$,

x) $(C_{1\text{-}6}alkyl)CN$, CN, $CH=C(R)_2$, $(CH_2)_pOH$, $C(=O)CHR_{13}$, $C(=NR_{13})R_{13}$, $NR_{10}C(=X_1)R_{13}$; or

vi) $C_{5\text{-}10}$ heterocycle optionally substituted with 1-3 groups of R_7, which may be attached through either a carbon or a heteroatom;

A represents NR, O, or S(O)p;

represents aryl or heteroaryl, heterocycle, heterocyclyl or heterocyclic, provided that in the case of a heteroaryl, heterocycle, heterocyclyl or heterocyclic, the cyclopropyl is not attached to a nitrogen atom on the ring;

R_x represents hydrogen or C_{1-6} alkyl;

R_3 represent

i) $NR_{13}(C=X_2)R_{12}$,

ii) $NR_{13}(C=X_1)R_{12}$,

iii) $NR_{13}SO_2R_{14}$,

iv) $N(R_{13})$heteroaryl,

v) $NR_{13}(CHR_{13})_{0-4}$aryl,

vi) $NR_{13}(CHR_{13})_{0-4}$heteroaryl,

vii) $S(CHR_{13})_{0-4}$aryl,

viii) $S(CHR_{13})_{0-4}$heteroaryl,

ix) $O(CHR_{13})_{0-4}$aryl,

x) $O(CHR_{13})_{0-4}$heteroaryl,

xi) $NOH(C=X_1)R_{12}$,

xii) -OC=N(OCOaryl) C_{1-6} alkyl

xiii) -OC=N(OH) C_{1-6} alkyl

xiv) C_{5-10} heteroaryl which may be attached through either a carbon or a heteroatom; said aryl and heteroaryl optionally substituted with 1-3 groups of R_7,

R_4, and R_{4a}, independently represent

v) hydrogen,

vi) halogen,

vii) C_{1-6} alkoxy, or

viii) C_{1-6} alkyl

r and s independently are 1-3, with the provision that when $(R_{4a})_s$ and $(R_4)_r$ are attached to an Ar or HAr ring the sum of r and s is less than or equal to 4;

R_5 and R_6 independently represent

xiii) hydrogen,

xiv) C_{1-6} alkyl optionally substituted with 1-3 groups of halogen, CN, OH, C_{1-6} alkoxy, amino, imino, hydroxyamino, alkoxyamino, C_{1-6} acyloxy, C_{1-6} alkylsulfenyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, aminosulfonyl, C_{1-6} alkylaminosulfonyl, C_{1-6} dialkylaminosulfonyl, 4-morpholinylsulfonyl, phenyl, pyridine, 5-isoxazolyl, ethylenyloxy, or ethynyl, said phenyl and pyridine optionally substituted with 1-3 halogen, CN, OH, CF_3, C_{1-6} alkyl or C_{1-6} alkoxy;

xv) C_{1-6} acyl optionally substituted with 1-3 groups of halogen, OH, SH, C_{1-6} alkoxy, naphthalenoxy, phenoxy, amino, C_{1-6} acylamino, hydroxylamino, alkoxylamino, C_{1-6} acyloxy, aralkyloxy, phenyl, pyridine, C_{1-6} alkylcarbonyl, C_{1-6} alkylamino, C_{1-6} dialkylamino, C_{1-6} hydroxyacyloxy, C_{1-6} alkylsulfenyl, phthalimido, maleimido, succinimido, said phenoxy, phenyl and pyridine optionally substituted with 1-3 groups of halo, OH, CN, C_{1-6} alkoxy, amino, C_{1-6} acylamino, CF_3 or C_{1-6} alkyl;

xvi) C_{1-6} alkylsulfonyl optionally substituted with 1-3 groups of halogen, OH, C_{1-6} alkoxy, amino, hydroxylamino, alkoxylamino, C_{1-6} acyloxy, or phenyl; said phenyl optionally substituted with 1-3 groups of halo, OH, C_{1-6} alkoxy, amino, C_{1-6} acylamino, CF_3 or C_{1-6} alkyl;

xvii) arylsulfonyl optionally substituted with 1-3 of halogen, C_{1-6} alkoxy, OH or C_{1-6} alkyl;

xviii) C_{1-6} alkoxycarbonyl optionally substituted with 1-3 of halogen, OH, C_{1-6} alkoxy, C_{1-6} acyloxy, or phenyl, said phenyl optionally substituted with 1-3 groups of halo, OH, C_{1-6} alkoxy, amino, C_{1-6} acylamino, CF_3 or C_{1-6} alkyl;

xix) aminocarbonyl, C_{1-6} alkylaminocarbonyl or C_{1-6} dialkylaminocarbonyl, said alkyl groups optionally substituted with 1-3 groups of halogen, OH, C_{1-6} alkoxy or phenyl

xx) five to six membered heterocycles optionally substituted with 1-3 groups of halogen, OH, CN, amino, C_{1-6} acylamino, C_{1-6} alkylsulfonylamino, C_{1-6} alkoxycarbonylamino, C_{1-6} alkoxy, C_{1-6} acyloxy or C_{1-6} alkyl, said alkyl optionally substituted with 1-3 groups of halogen, or C_{1-6} alkoxy;

xxi) C_{3-6} cycloalkylcarbonyl optionally substituted with 1-3 groups of halogen, OH, C_{1-6} alkoxy or CN;

xxii) benzoyl optionally substituted with 1-3 groups of halogen, OH, C1-6 alkoxy, C1-6 alkyl, CF_3, C1-6 alkanoyl, amino or C1-6 acylamino;

xxiii) pyrrolylcarbonyl optionally substituted with 1-3 of C1-6 alkyl;

xxiv) C1-2 acyloxyacetyl where the acyl is optionally substituted with amino, C1-6 alkylamino, C1-6 dialkylamino, 4-morpholino, 4-aminophenyl, 4-(dialkylamino)phenyl, 4-(glycylamino)phenyl; or

R5 and R6 taken together with any intervening atoms can form a 3 to 7 membered heterocyclic ring containing carbon atoms and 1-2 heteroatoms independently chosen from O, S, SO, SO_2, N, or NR_8;

R7 represent

iii) hydrogen, halogen, CN, CO_2R, $CON(R)_2$, CHO, CH_2NHAc, C(=NOR), OH, C1-6 alkoxy, C1-6 alkyl, alkenyl, hydroxy C1-6 alkyl, $(CH_2)_{1-3}NHC(O)$C1-6 alkyl, $(CH_2)_{1-3}N$(C1-6 alkyl)$_2$

iv) $(CH_2)_n$amino, $(CH_2)_n$C1-6 alkylamino, C1-6 dialkylamino, hydroxylamino or C1-2 alkoxyamino all of which can be optionally substituted on the nitrogen with C1-6 acyl, C1-6 alkylsulfonyl or C1-6 alkoxycarbonyl, said acyl and alkylsulfonyl optionally substituted with 1-2 of halogen or OH;

R8 and R9 independently represents

iv) H, CN,

v) C1-6 alkyl optionally substituted with 1-3 halogen, CN, OH, C1-6 alkoxy, C1-6 acyloxy, or amino,

vi) phenyl optionally substituted with 1-3 groups of halogen, OH, C1-6 alkoxy; or

R7 and R8 taken together can form a 3-7 membered carbon ring optionally interrupted with 1-2 heteroatoms chosen from O, S, SO, SO_2, NH, and NR_8;

X1 represents O, S or NR13, NCN, NCO_2R_{16}, or NSO_2R_{14}

X2 represents O, S, NH or NSO_2R_{14};

R10 represents hydrogen, C1-6 alkyl or CO_2R_{15};

R_{12} represents hydrogen, C_{1-6} alkyl, NH_2, OR, CHF_2, $CHCl_2$, CR_2Cl, $(CH_2)_nSR$, $(CH_2)_nCN$, $(CH_2)_nSO_2R$, $(CH_2)_nS(O)R$, C_{1-6} alkylamino, C_{5-10} heteroaryl or C_{1-6} dialkylamino, where said alkyl may be substituted with 1-3 groups of halo, CN, OH or C_{1-6} alkoxy, said heteroaryl optionally substituted with 1-3 groups of R_7;

Each R_{13} represents independently hydrogen, C_{1-6} alkyl, C_{6-10} aryl, NR_5R_6, SR_8, $S(O)R_8$, $S(O)_2R_8$, CN, OH, C_{1-6} alkylS(O)R, C_{1-6} alkoxycarbonyl, hydroxycarbonyl, -OCOaryl, C_{1-6} acyl, C_{3-7} membered carbon ring optionally interrupted with 1-4 heteroatoms chosen from O, S, SO, SO_2, NH and NR_8 where said C_{1-6} alkyl, aryl or C_{1-6} acyl groups may be independently substituted with 0-3 halogens, hydroxy, $N(R)_2$, CO_2R, C_{6-10} aryl, C_{5-10} heteroaryl, or C_{1-6} alkoxy groups;
When two R_{13} groups are attached to the same atom or two adjacent atoms they may be taken together to form a 3-7 membered carbon ring optionally interrupted with 1-2 heteroatoms chosen from O, S, SO, SO_2, NH, and NR_8;

R represents hydrogen or C_{1-6} alkyl;

R_{14} represents amino, C_{1-6} alkyl, C_{1-6} haloalkyl, five to six membered heterocycles or phenyl, said phenyl and heterocycles optionally substituted with 1-3 group of halo, C_{1-6} alkoxy, C_{1-6} acylamino, or C_{1-6} alkyl, hydroxy and/or amino, said amino and hydroxy optionally protected with an amino or hydroxy protecting group;

R_{15} is C_{1-6} alkyl or benzyl said benzyl optionally substituted with 1-3 groups of halo, OH, C_{1-6} alkoxy, amino, C_{1-6} acylamino, or C_{1-6} alkyl;

R_{16} is hydrogen, C_{5-10}heteroaryl, C_{6-10}aryl, said heteroaryl and aryl optionally substituted with 1-3 groups of R_7;

p represents 0-2 and

m, n, and q represents 0-1.

2. A compound according to claim 1 wherein R_1 represents H, NR_5R_6, CN, OH, $C(R)_2OR_{14}$, $NHC(=X1)N(R_{13})_2$, $C(=NOH)N(R_{13})_2$, $NR_{10}C(=X_1)R_{13}$ or $CR_7R_8R_9$.

3. A compound according to claim 1 wherein 

is phenyl, pyridine, pyrimidine, or piperidine.

4. A compound according to claim 1 wherein R_1 is NR_5R_6.

5. A compound according to claim 1 wherein R_1 is CN.

6 A compound according to claim 1wherein one of is $NR_{10}C(=X_1)R_{13}$.

7. A compound according to claim 1 wherein R3 is $NR(C=X_1)R_{12}$, C_{5-10} heteroaryl, $NH(CH_2)_{0-4}$aryl, $NH(CH_2)_{0-4}$heteroaryl, said aryl and heteroaryl optionally substituted with 1-3 groups of Ra.

8. A compound according to claim 7 wherein R3 is a C_{5-10} heteroaryl represented by 

which represents an optionally substituted aromatic heterocyclic group containing 1to 4 nitrogen atoms and at least one double bond, and which is connected through a bond on any nitrogen.

9. A compound according to claim 1 wherein R_5 and R_6 independently are:

v) H,

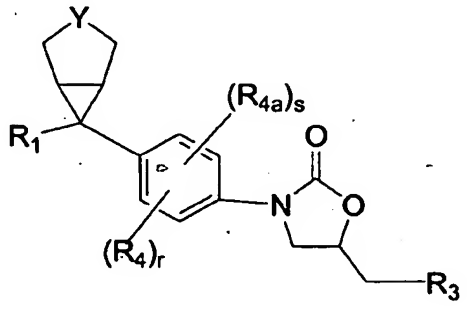
vi) C_{1-6} alkyl optionally substituted with 1-3 groups of halogen, CN, OH, C_{1-6} alkoxy, amino, hydroxyamino, alkoxyamino, C_{1-6} acyloxy, C_{1-6} alkylsulfenyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, aminosulfonyl, C_{1-6} alkylaminosulfonyl, C_{1-6} dialkylaminosulfonyl, 4-morpholinylsulfonyl, phenyl, pyridine, 5-isoxazolyl, ethyenyloxy, or ethynyl, said phenyl and pyridine optionally substituted with 1-3 halogen, CN, OH, CF_3, C_{1-6} alkyl or C_{1-6} alkoxy;

vii) C_{1-6} acyl optionally substituted with 1-3 groups of halogen, OH, SH, C_{1-6} alkoxy, naphthalenoxy, phenoxy, amino, C_{1-6} acylamino, hydroxylamino, alkoxylamino, C_{1-6} acyloxy, phenyl, pyridine, C_{1-6} alkylcarbonyl, C_{1-6} alkylamino, C_{1-6} dialkylamino, C_{1-6} hydroxyacyloxy, C_{1-6} alkylsulfenyl, phthalimido, maleimido, succinimido, said phenoxy, phenyl and pyridine optionally substituted with 1-3 groups of halo, OH, CN, C_{1-6} alkoxy, amino, C_{1-6} acylamino, CF_3 or C_{1-6} alkyl; or

viii) benzoyl optionally substituted with 1-3 groups of halogen, OH, C_{1-6} alkoxy, C_{1-6} alkyl, CF3, C_{1-6} alkanoyl, amino or C_{1-6} acylamino and all other variables are as described herein.

10. A compound according to claim 1 wherein X_1 represents O.

11. A compound according to claim 1 wherein the structural formula is II:



Formula II

wherein R_1, R_4, R_{4a}, Y and R_3 are as described above.

12. A compound which is:
N-[5(S)-3-[4-[(1α,5α,6β)-(6-cyanobicyclo[3.1.0]hexan-6-yl)]phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide,
1-[5(R)-3-[4-[(1α,5α,6β)-(6-cyanobicyclo[3.1.0]hexan-6-yl)]phenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole,
N-[5(S)-3-[4-[(1α,5α,6β)-(3-t-butoxycarbonyl-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl)]phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide,

N-[5(S)-3-[4-[(1α,5α,6β)-(6-cyano-3-azabicyclo[3.1.0]hexan-6-yl)]phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide hydrochloride,
1-[5(R)-3-[4-[(1α,5α,6β)-(3-t-butoxycarbonyl-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl)]phenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole,
1-[5(R)-3-[4-[(1α,5α,6β)-(6-cyano-3-azabicyclo[3.1.0]hexan-6-yl)]phenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole hydrochloride,
N-[5(S)-3-[4-[(1α,5α,6β)-(3-acetoxyacetyl-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl)]phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide,
N-[5(S)-3-[4-[(1α,5α,6β)-(6-cyano-3-hydroxyacetyl-3-azabicyclo[3.1.0]hexan-6-yl)]phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide,
N-[5(S)-3-[4-[(1α,5α,6β)-(6-cyano-3-methanesulfonyl-3-azabicyclo[3.1.0]hexan-6-yl)]phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide,
N-[5(S)-3-[4-[(1α,5α,6β)-(6-cyano-3-methyl-3-azabicyclo[3.1.0]hexan-6-yl)]phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide,
N-[5(S)-3-[4-[(1α,5α,6β)-(3,6-dicyano-3-azabicyclo[3.1.0]hexan-6-yl)]phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide,
N-[5(S)-3-[4-[(1α,5α,6β)-(6-cyano-3-cyanomethyl-3-azabicyclo[3.1.0]hexan-6-yl)]phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide,
5(R)-3-[4-[(1α,5α,6β)-(3-t-butoxycarbonyl-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl)]phenyl]-5-[(isoxazol-3-yl)oxy]methyloxazolidin-2-one, 5(R)-3-[4-[(1α,5α,6β)-(6-cyano-3-azabicyclo[3.1.0]hexan-6-yl)]phenyl]-5-[(isoxazol-3-yl)oxy]methyloxazolidin-2-one hydrochloride,
5(R)-3-[4-[(1α,5α,6β)-(3-t-butoxycarbonyl-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl)]phenyl]-5-[N-(t-butoxycarbonyl)-N-(isoxazol-3-yl)]aminomethyloxazolidin-2-one,
5(R)-3-[4-[(1α,5α,6β)-(6-cyano-3-azabicyclo[3.1.0]hexan-6-yl)]phenyl]-5-[N-(isoxazol-3-yl)]aminomethyloxazolidin-2-one hydrochloride,

or

its enantiomer, diastereomer, or pharmaceutically acceptable salt, hydrate or prodrug thereof.

13. A pharmaceutical composition comprised of a compound in accordance with claim 1 in combination with a pharmaceutically acceptable carrier.

14. A pharmaceutical composition produced by combining a compound in accordance with claim 1 with a pharmaceutically acceptable carrier.

15. A method of treating or preventing a bacterial infection in a mammalian patient in need thereof, comprising administering to said patient an effective amount of a compound of claim 1.

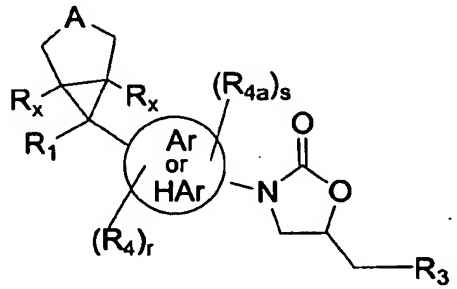
ABSTRACT OF THE DISCLOSURE

TITLE OF THE INVENTION

Oxazolidinone Antibiotics and Derivatives Thereof

This invention relates to new oxazolidinones having a cyclopropyl moiety, which are effective against aerobic and anerobic pathogens such as multi-resistant staphylococci, streptococci and enterococci, Bacteroides spp., Clostridia spp. species, as well as acid-fast organisms such as *Mycobacterium tuberculosis* and other mycobacterial species.

The compounds are represented by structural formula I:



I

its enantiomer, diastereomer, or pharmaceutically acceptable salt or ester thereof.